I5Q-MC-CGAW Statistical Analysis Plan Version 2

A Randomized, Double-Blind, Placebo-Controlled Study of Galcanezumab in Adults with Treatment-Resistant Migraine – the CONQUER Study

NCT03559257

Approval Date: 08-Jul-2019

1. Statistical Analysis Plan for Protocol I5Q-MC-CGAW: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Galcanezumab in Adults with Treatment-Resistant Migraine – the CONQUER Study

LY2951742 (Galcanezumab)

I5Q-MC-CGAW is a Phase 3, multisite, double-blind, randomized, placebo-controlled 3-month study to compare the efficacy and safety of LY2951742 in preventing migraine headaches in treatment resistant patients suffering from episodic or chronic migraine. Patients may continue into a 3-month open-label extension following the double-blind treatment period.

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Statistical Analysis Plan Version 1 was electronically signed and approved by Lilly on 31-Jul-2018

Statistical Analysis Plan Version 2 was electronically signed and approved by Lilly on the date provided below.

Approval Date: 08-Jul-2019 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

3. Revision History

Statistical Analysis Plan Version 2 was approved prior to the first database lock and interim analysis (analysis for primary efficacy endpoint assessment after all patients have completed the double-blind phase, which is the first unblinding to the study team). The changes incorporated in Version 2 are summarized as follows:

- Updated safety analyses for the open-label extension (Study Period IV) to reflect new industry-wide guidelines for standard safety analyses for individual trials. Safety analyses specific to SP IV in the open-label population have been replaced with analyses evaluating galcanezumab (GMB)-treated time in the GMB-treated population. This analysis method provides overall estimates of safety outcomes regardless of study phase. Due to this change, the patient population, baseline, and postbaseline definitions for safety parameters in Table CGAW.5.4 and all related safety sections were updated accordingly.
- Clarified the definition of a non-responder for the proportion of patients who continue to demonstrate >=50% response for all 3 months in the open-label treatment period.
- Added definition of weekly baseline number of migraine headache days for analysis of the number of weekly migraine headache days in Month 1.
- Removed language regarding subgroup analysis for elderly patients (>=65 year of age) since minimum number of patients needed for this analysis (>=10% of total sample) was not met.
- Expanded list of baseline disease state characteristics to be reported.
- Clarified list of analyses from the open-label treatment period that will be included in the interim analysis.
- Added summary of treatment compliance for SP IV.
- Clarified definition for prior therapy failures during the past 10 years.
- Updated references.

4. Study Objectives

Table CGAW.4.1 shows the key objectives and endpoints of the study.

Table CGAW.5.1 provides definitions for the terms referenced below.

Table CGAW.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objective To test the hypothesis that galcanezumab is superior to placebo in the prevention of migraine in patients with treatment-resistant migraine	The overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase in the total population (episodic and chronic migraine)[a]
Key Secondary Objectives **Note:** All key secondary objectives will be tested in both the total population (episodic and chronic migraine) and the episodic migraine subpopulation unless otherwise specified.	The specific methodology (including testing order and population) for the tests of the following key secondary endpoints is specified in Section 5.5.10.4:
• To compare galcanezumab with placebo with respect to prevention of migraine in the episodic migraine subpopulation	• The overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase in patients with episodic migraine
• To compare galcanezumab with placebo with respect to 50% response rate	• The percentage of patients with ≥50% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in functioning	• The mean change from baseline in the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) at Month 3
• To compare galcanezumab with placebo with respect to 75% response rate	• The percentage of patients with ≥75% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to 100% response rate	• The percentage of patients with 100% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase

(Table CGAW.4.1. continued)

Objectives	Endpoints
Secondary Objectives **Note:** All other secondary objectives will be tested in both the total population (episodic and chronic migraine) and the episodic migraine subpopulation unless otherwise specified.	
• To compare galcanezumab with placebo with respect to onset of effect	• The initial month at which statistical separation in mean change from baseline in the number of monthly migraine headache days is demonstrated and maintained at all subsequent months through Month 3 in the double-blind treatment phase • If the initial month of onset is Month 1, then the initial week at which statistical separation in mean change from baseline in the number of weekly migraine headache days is demonstrated and maintained at all subsequent weeks during Month 1
• To compare galcanezumab with placebo with respect to change in use of acute headache treatment	• The overall mean change from baseline in the number of monthly days with acute headache medication use during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in monthly headache days	• The overall mean change from baseline in the number of monthly headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in International Classification of Headache Disorders (ICHD) migraine headache days	• The overall mean change from baseline in the number of monthly International Classification of Headache Disorders (ICHD) migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in monthly migraine headache hours	• The overall mean change from baseline in the number of monthly migraine headache hours during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to change in monthly headache hours	• The overall mean change from baseline in the number of monthly headache hours during the 3-month double-blind treatment phase

(Table CGAW.4.1. continued)

Objectives	Endpoints
Secondary Objectives (continued)	
• To compare galcanezumab with placebo with respect to changes in disability and quality of life	• Changes from baseline to Month 3 on the following measures: o Migraine Disability Assessment (MIDAS) total score and individual items o MSQ v2.1 total score, and Role Function-Preventive and Emotional Function domain scores o Health Care Resource Utilization (HCRU) and Employment Status o European Quality of Life Questionnaire 5-Dimensions 5-Levels (EQ-5D-5L) o Migraine Interictal Burden Scale (MIBS-4) o Work Productivity and Activity Impairment Questionnaire (WPAI)
• To compare galcanezumab with placebo with respect to change in patient global impression of the severity of migraine	• Mean change from baseline in the Patient Global Impression of Severity (PGI-S) score at Month 3
• To compare galcanezumab with placebo with respect to changes in migraine attacks (episodic migraine subpopulation only)	• The overall mean change from baseline in the number of monthly migraine attacks during the 3-month double-blind treatment phase in patients with episodic migraine
• To compare galcanezumab with placebo with respect to 30% response rate (chronic migraine subpopulation only)	• The percentage of chronic migraine patients with ≥30% reduction from baseline in monthly migraine headache days during the 3-month double-blind treatment phase
• To compare galcanezumab with placebo with respect to safety and tolerability[b]	• Analysis of: o treatment-emergent adverse events (TEAEs) o serious adverse events (SAEs) o discontinuation due to AEs o discontinuation rates o vital signs and weight o electrocardiograms (ECGs) o laboratory measures
• To assess changes in efficacy, safety, and functional outcomes during Study Period IV (open-label treatment)	• In Study Period IV: o Mean changes in all continuous measures of efficacy, safety, and functional outcomes that are also assessed in the double-blind phase o Among patients previously treated with galcanezumab who meet 50% response criteria at Month 3 in the double-blind treatment phase, the proportion of patients who demonstrate 50% response for all 3 months in the open-label treatment phase

(Table CGAW.4.1. continued)

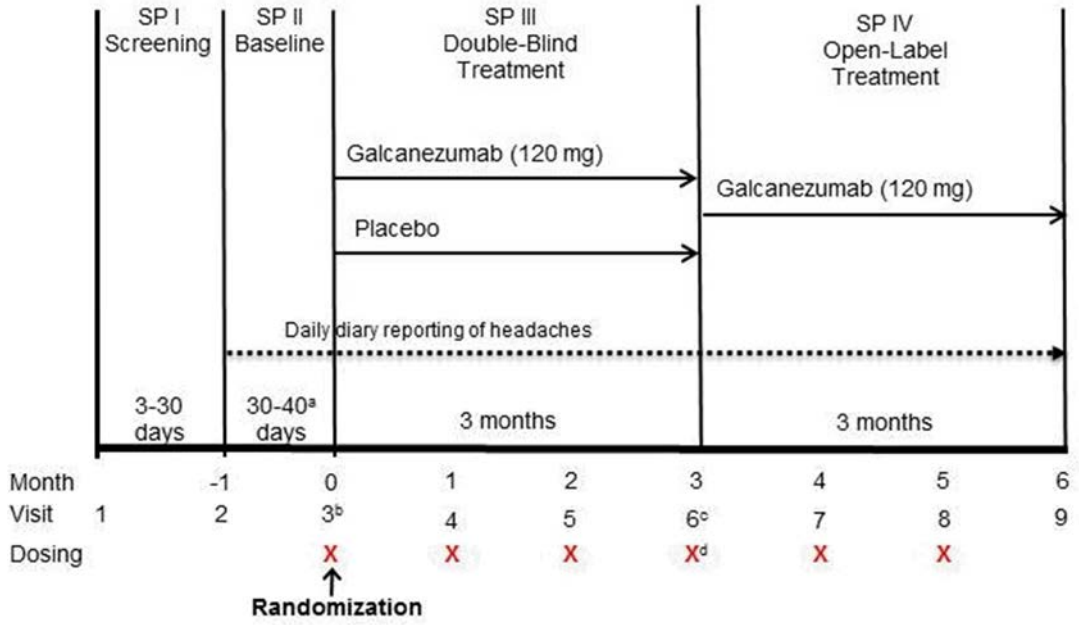
Objectives	Endpoints
Tertiary Objectives **Note:** All tertiary objectives will be tested in both the total population (episodic and chronic migraine) and the episodic migraine subpopulation.	
• To compare galcanezumab with placebo with respect to changes in symptoms associated with migraine	• Change from baseline in the number of monthly migraine headache days with: o nausea and/or vomiting o photophobia and phonophobia o aura o prodromal symptoms • Change from baseline in the number of monthly symptom-free days and headache-free days
• CCI [redacted]	[redacted]
• To explore use of comfort measures at the injection site	• Descriptive summary of comfort measures used

[a] Episodic migraine is defined as 4 to 14 migraine headache days and <15 headache days per 30-day period in the prospective baseline period. In the event that there are any patients with 4 to <8 migraine headache days and 15-29 headache days per 30-day period in the prospective baseline period, they will be considered to have episodic migraine. Chronic migraine is defined as 15-29 headache days per 30-day period in the prospective baseline period, of which at least 8 are migraine.

[b] Note that safety analyses will be conducted for the total safety population only.

5. A Priori Statistical Methods

5.1. Study Design



Abbreviation: SP = study period.

[a] Eligibility period determined between a minimum of 30 days and a maximum of 40 days, with up to 5 additional days to schedule randomization visit, if necessary.

[b] Patients randomized to galcanezumab will receive a loading dose of 240 mg at the first injection only (Visit 3).

[c] Patients randomized to placebo who enter SP IV will receive a loading dose of galcanezumab 240 mg at the first injection only of SP IV (Visit 6).

[d] First injection of the open-label treatment phase will occur at Visit 6 once all study procedures for the double-blind phase are completed.

Figure CGAW.5.1. Illustration of study design for Clinical Protocol I5Q-MC-CGAW.

5.2. Determination of Sample Size

The study will enroll approximately 420 patients. Eligible patients will be randomized in a blinded fashion in a 1:1 ratio to placebo or galcanezumab (120 mg with a loading dose of 240 mg). With the assumption of a 10% discontinuation rate and an effect size of 0.39, it is estimated that this sample size will provide approximately 96% power that galcanezumab will separate from placebo at a 2-sided significance level of 0.05 for the intent-to-treat (ITT) population in this study.

The study is also powered for the subpopulation of patients with episodic migraine. The study will seek to enroll approximately 250 patients with episodic migraine as determined during the prospective baseline period (approximately 60% of the total population). With the assumption of a 10% discontinuation rate and an effect size of 0.46, it is estimated that this will provide

approximately 93% power that galcanezumab will separate from placebo at a 2-sided significance level of 0.05 for the episodic migraine sub-population in this study.

Assumptions in this sample size calculation were based on data from 3 double-blind, placebo-controlled, phase 3 studies, with an adjustment made to reflect differences in this study and the potential impact of the development phase and the inclusion of an open-label treatment phase on placebo responses.

5.3. Randomization and Treatment Assignment

Patients will be randomized in a 1:1 ratio to placebo and galcanezumab 120 mg/month. Randomization will be stratified within country and migraine frequency in the prospective baseline period (low frequency episodic, high frequency episodic, and chronic).

- Low frequency episodic migraine is defined as 4 to <8 migraine headache days and <=29 headache days per 30-day period.
- High frequency episodic migraine is defined as 8 to 14 migraine headache days and <15 headache days per 30-day period.
- Chronic migraine is defined as ≥8 migraine headache days and with 15-29 headache days per 30-day period.

To ensure an appropriate balance of patients with episodic and chronic migraine, the sponsor will stop enrollment of patients with chronic migraine if the number of patients exceeds approximately 40% of the total sample size.

5.4. Endpoints

5.4.1. Efficacy Endpoints

Migraine and headache endpoints are defined in Table CGAW.5.1. Each month is defined as a 30-day period with migraine or headache measures normalized from the visit intervals.

Table CGAW.5.1. Migraine and Headache Endpoint Definitions

Diagnosis	Definition/Criteria
Migraine headache	A headache, with or without aura, of ≥30 minutes duration with both of the following required features (A and B): A. At least 2 of the following headache characteristics: • Unilateral location • Pulsating quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity AND B. During headache at least one of the following: • Nausea and/or vomiting • Photophobia and phonophobia *(Definition adapted from the standard IHS ICHD-3 definition)*
Probable migraine headache	A headache of ≥30 minutes duration, with or without aura, but missing one of the migraine features in the IHS ICHD-3 definition (ICHD-3 2013). To be exact, it meets either at least two A criteria and zero B criteria, or one A criteria and at least one B criteria.
Migraine headache day (primary objective)	A calendar day on which a migraine headache or probable migraine headache occurs.
ICHD migraine headache day	A calendar day on which a migraine headache occurs.
Migraine headache attack	Beginning on any day a migraine headache or probable migraine headache is recorded and ends when a migraine-free day occurs.
Non-migraine headache	All headaches of ≥30 minutes duration not fulfilling the definition of migraine or probable migraine.
Non-migraine headache day	A calendar day on which a non-migraine headache occurs.
Headache day	A calendar day on which any type of headache occurs (including migraine, probable migraine, and non-migraine headache).

Abbreviations: ICHD = International Classification of Headache Disorders; IHS = International Headache Society.

Headache information will be collected via an electronic patient-reported outcomes (ePRO) diary. Patients will need to enter ePRO diary data daily beginning from Visit 2 and continuing until Visit 9.

Information recorded in the ePRO diary, the possible responses and the assignment to the type of headache is presented in Table CGAW.5.2.

Table CGAW.5.2. ePRO Diary Questions, Responses, and Assignment to Headache Type

QUESTION	RESPONSES	HEADACHE ASSIGNMENT
Q1. Yesterday, did you have a headache that lasted for thirty minutes or more?	Yes	Migraine if at least 2 migraine Criteria As and at least 1 migraine Criterion B are met; or meets either at least two A criteria and zero B criteria, or one A criteria and at least one B criterion.
	No[a]	
Q2. Enter the total number of hours you had a headache yesterday.	Range 1 to 24	If ≥1 the headache will be counted as a headache day.
Q3. Yesterday, what was the worst headache pain?	Mild	
	Moderate	Migraine Criteria A
	Severe	Migraine Criteria A
Q4. Yesterday, was the headache throbbing or pounding?	Yes	Migraine Criteria A
	No	
Q5. Yesterday, was the headache just on the right or left side of your head?	Yes	Migraine Criteria A
	No	
Q6. Yesterday, was the headache made worse by your usual daily activity?	Yes	Migraine Criteria A
	No	
Q7. Yesterday, did the headache come with sensitivity to light and sound?	Yes	Migraine Criteria B
	No	
Q8. Yesterday, did you feel sick to the stomach or throw-up with the headache?	Yes	Migraine Criteria B
	No	
Q9. Yesterday, did you have your menstrual period (if female)?	Yes	
	No	
Q10. Yesterday, did you experience aura?	Yes	
	No	
Q11. Yesterday, did you experience any warning symptoms (prodrome symptoms) that a migraine was coming other than aura?	Yes	
	No	
Q12. Yesterday, did you take any medicine for your headache?	Yes	Medication will only count as headache medication on a day a headache occurred.
	No	

[a] If "No" is answered for Q1, then the patients will skip Q2 - Q6, only answer questions Q7 - Q12 by removing reference to headache.

Primary Measure: Number of Migraine Headache Days

The primary measure is the number of monthly migraine headache days (per 30-day period). A migraine headache day is defined as a calendar day on which a **migraine or probable migraine** occurs.

The number of monthly migraine headache days in each 30-day period will be summarized from daily data for each patient in that period (including approximately 30 days of daily data from the baseline period prior to randomization, 3 months of daily data during double-blind treatment phase, 3 months of daily data during open-label treatment phase).

The daily data will reflect whether the patients meet the migraine / probable migraine criteria; those data will be aggregated, and the number of migraine headache days will be provided for each of the 30-day periods. In calculating the number of migraine headache days for each period, if the period is not equal to 30 days, the number of migraine headache days will be adjusted by multiplying the number of migraine headache days by (30/x) where 'x' is the total number of non-missing diary days in the period.

This approach to missing ePRO diary data assumes that the rate of migraine headache per day is the same for days with missing and non-missing ePRO diary days. The same approach will also be applied to secondary and exploratory efficacy measures that are derived from ePRO data.

Additionally, if the compliance rate for a monthly interval is ≤50%, then all endpoints to be derived from the ePRO diary data for that 1-month period will be considered missing. The compliance rate will be calculated as described in Section 5.5.7.

Other Secondary and Exploratory Efficacy Measures

The same approach for adjusting the number of days within each period to a 30-day period and the same approach to imputing monthly data based on compliance as for the primary measure will be applied to all efficacy measures that are derived from ePRO diary data and need normalization to a 30-day period, including:

- **Number of ICHD migraine headache days** is calculated as the number of calendar days in a 30-day period on which a migraine occurs. Probable migraine is excluded.
- **Number of headache days** is calculated as the number of calendar days in a 30-day period on which a headache occurs.
- **Number of migraine headache hours** is calculated as the total number of headache hours in a 30-day period on days when a migraine or probable migraine occurs.
- **Number of headache hours** is calculated as the total number of headache hours in a 30-day period on which a headache occurred.
- **Number of days with acute headache medication use** is calculated as the number of calendar days in a 30-day period on which abortive medication is used.

- **Number of migraine attacks** is calculated as the number of sets of consecutive migraine headache days separated by at least 1 migraine **headache-free** day in a 30-day period. For example, a migraine headache day starting on 5JAN and ending on 6JAN will result in a migraine headache free day on 7JAN (assuming that it is not a migraine headache day on 7JAN). This will count as 1 migraine attack that started on 5JAN and ended on 6JAN. For a migraine attack that begins in 1 30-day period but ends in another, only 1 migraine attack will be counted in the first of the 2 periods. For example, in the case of 7 days of consecutive migraine headache days with 3 days in baseline period and 4 days in Month 1, only 1 migraine attack will be counted in the baseline period; the 4 days of migraine headache days in Month 1 will not be counted as migraine attack in Month 1.
  This measure (number of migraine attacks) is needed for the episodic migraine subpopulation only.

Additional secondary and exploratory efficacy measures will be derived as follows:

- **Percent change from baseline in the number of migraine headache days** will be calculated for any postbaseline 30-day period as:

$$-1 * \frac{100 \times (\#\text{ of MHD in Month Y} - \#\text{ of MHD in baseline period})}{\#\text{ of MHD in baseline period}}$$

- An **X% responder** is defined as Yes, if any patient who has a ≥X% reduction in the total number of migraine headache days in a 30-day period relative to baseline period, as No if otherwise. Therefore, if the percent change from baseline in the number of migraine headache days is ≥X%, the patient will be counted as an X% responder. In other words, if the response rate defined above in a month is ≥X%, then the patient will be an X% responder in that month. Indicators of X% responders will be derived for X=30, 50, 75, and 100.

- P**roportion of patients who continue to demonstrate >=50% response for all 3 months in the open-label treatment period**. This analysis will include patients previously treated with galcanezumab who met 50% response criteria at Month 3 in the double-blind treatment phase (SP III) and entered the open-label treatment phase (SP IV). If a patient has missing data due to either early discontinuation or diary non-compliance such that response cannot be calculated for each of the 3 months in the open-label treatment period, then the patient will be considered a non-responder.

- **Number of migraine headache days with photophobia and phonophobia** is calculated as the total number of migraine headache days with an answer of "yes" to Q7 in a 30-day period.

- **Number of migraine headache days with nausea and/or vomiting** is calculated as the total number of migraine headache days with an answer of "yes" to Q8 in a 30-day period.

- **Number of migraine headache days with aura** is calculated as the total number of migraine headache days with an answer of "yes" to Q10 in a 30-day period.

- **Number of migraine headache days with prodrome symptoms other than aura** is calculated as the total number of migraine headache days with an answer of "yes" to Q11 in a 30-day period.
- **Number of monthly symptom-free and headache-free days** is calculated as the total number of days with no headache and no headache symptoms in a 30-day period, i.e., the answers to Questions 1, 7, 8, 10, and 11 are all "No"**.**
- **Number of weekly migraine headache days in Month 1** is calculated as the number of migraine headache days in a 7-day period on which a migraine headache occurs. At month 1, the first 7 calendar days will be counted as week 1, the second 7 calendar days will be counted as week 2, the third 7 calendar days will be counted as week 3, and the rest of days will be counted as week 4.
- **Number of days with triptan use** is calculated as the number of days with Triptan use during a 30-day period.
- **Number of days with NSAIDs/aspirin use** is calculated as the number of days with NSAIDs/aspirin use during a 30-day period.
- **Number of days with acetaminophen/paracetamol use** is calculated as the number of days with acetaminophen/paracetamol use during a 30-day period.
- **Number of days with ergot use** is calculated as the number of days with ergot use during a 30-day period.
- **Number of days with anti-nausea medication use** is calculated as the number of days with anti-nausea medication use during a 30-day period.
- **Number of days with opioids and barbiturates use** is calculated as the number of days with opioids and barbiturates use during a 30-day period.

5.4.2. Other Efficacy Measures

5.4.2.1. Patient Global Impression

The Patient Global Impression of Severity (PGI-S) will be collected at baseline (Visit 3), the end of the double-blind treatment phase (Visit 6), and the end of the open-label treatment phase (Visit 9). In this single-item scale, patients rate the severity of their migraine condition on a scale ranging from "not at all ill" (coded as 1) to "extremely ill" (coded as 7).

Change from baseline in PGI-S scores will be summarized and analyzed.

5.4.3. Health Outcome Questionnaires

The following health outcome questionnaires are collected using patient direct data entry on an electronic device which does not allow patients to skip items. Patients either complete each scale in its entirety or not at all. Therefore, no imputation for missing values is necessary for these scales.

5.4.3.1. Migraine Specific Quality of Life (MSQ) v2.1

Migraine Specific Quality of Life (MSQ) v2.1 consists of 14 questions. The questions measure the impact of migraine on health-related quality of life across 3 domains: 1) Role Function-Restrictive (7 questions), examines the degree to which performance of daily activities is limited by migraine; 2) Role Function-Preventive (4 questions), examines the degree to which performance of daily activities is prevented by migraine; 3) Emotional Function (3 questions), examines feelings of frustration and helplessness due to migraine.

Precoded item values and final item values for MSQ item responses are shown in Table CGAW.5.3. All item values range from 1 to 6. Final item values will be used for analysis with higher scores reflecting better quality of life.

Table CGAW.5.3. Item Values for Migraine Specific Quality of Life (MSQ) Item Responses

Response Categories	Precoded Item Value	Final Item Value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

Questions 1 to 7 of the questionnaire will be grouped together as Role Function-Restrictive domain, questions 8 to 11 as Role Function-Preventive domain and questions 12 to 14 as the Emotional Function domain.

The raw score of each domain will be calculated as the sum of the raw scores of each question in that domain. The total score will be calculated as the sum of Role Function-Restrictive, Role Function-Preventive, and Emotional Function domain scores.

The raw scores of each domain and the total score will be transformed to a 0 to 100 scale using the following formulae:

- Role Function-Restrictive (range of 7 to 42):

$$\frac{(\text{raw score} - 7)\text{x}100}{35}$$

- Role Function-Preventive (range of 4 to 24):

$$\frac{(\text{raw score} - 4)\text{x}100}{20}$$

- Emotional Function (range of 3 to 18):

$$\frac{(\text{raw score} - 3)\text{x}100}{15}$$

- Total Score (range of 14 to 84):

$$\frac{(\text{raw total score} - 14)\text{x}100}{70}$$

The transformed total score and domain scores will be analyzed.

5.4.3.2. MIDAS (Migraine Disability Assessment)

The Migraine Disability Assessment (MIDAS) is a patient-rated scale which was designed to quantify headache-related disability over a 3-month period. This instrument consists of 5 items that reflect the number of days reported as missed, or with reduced productivity at work or home and social events. Each question is answered as the number of days during the past 3 months of assessment, ranging from 0 to 90, with the total score being the summation of the 5 numeric responses. A higher value is indicative of more disability. This instrument is considered highly reliable and valid, and is correlated with clinical judgment regarding the need for medical care (Stewart et al. 1999, 2001). For clinical interpretability, 4 categorical grades were developed based on the total score: Grade I (0 to 5) is for little or no disability, Grade II (6 to 10) is for mild disability, Grade III (11 to 20) is for moderate disability, and Grade IV (21+) is for severe disability. The severe disability category has subsequently been subdivided into Grade IV-A (severe [21 to 40]) and Grade IV-B (very severe [41 to 270]) because a high proportion of patients with chronic migraine are in Grade IV (Blumenfeld et al. 2011).

MIDAS consists of 5 questions (Q1-Q5) and 2 additional questions (A and B). The questionnaire measures the impact that migraine headaches have on migraineurs' life, including days of work or school missed, days with productivity at work or school reduced to half or more, days with household work missed, days with productivity in household work reduced to half or more, and days missed family / social / leisure activities. Each question is answered as a number of days during the past 3 months of assessment, ranging from 0 to 90. The answers to all 5 questions will be added up to a total MIDAS score.

The total MIDAS score and item scores will be analyzed.

5.4.3.3. Health Care Resource Utilization (HCRU) and Employment Status

Health Care Resource Utilization (HCRU) will be solicited by study personnel while documenting patient responses. Data to be collected include:

- number of hospital emergency room (ER) visits
- number of overnight hospital stays
- number of other visits with healthcare professional
- number of hospital ER visits related to migraine headache
- number of overnight hospital stays related to migraine headache
- number of other visits with healthcare professional related to migraine headache

- number of times admitted to hospital
- number of time admitted to hospital related to migraine

Visits associated with their participation in the clinical trial should not be included in the responses. A question on employment status is also solicited, given the correlation and potential confounding with health outcomes measures.

At the baseline visit, these questions will be asked for the time frame of past 6 months. At postbaseline visits, the questions will be asked for the time from last visit to current visit.

Incidence rates (HCRU events per 100 patient years) will be calculated for different study periods.

HCRU data and employment status will be summarized; change from baseline in incidence rates will be analyzed.

5.4.3.4. Migraine Interictal Burden Scale (MIBS-4)

The Migraine Interictal Burden Scale (MIBS-4) measures the burden related to headache in the time between attacks. The self-administered instrument consists of 4 items that address disruption at work and school, diminished family and social life, difficulty planning, and emotional difficulty. The questionnaire specifically ask about the effect of the disease over the past 4 weeks on days without a headache attack. Response options include: don't know/not applicable (0), never (0), rarely (1), some of the time (2), much of the time (3), or most or all of the time (3). Each response has an associated numerical score, with the summation across all 4 items resulting in a total score ranging from 0 to 12, and the level of interictal burden being categorized into the following: 0 for none, 1-2 mild, 3-4 moderate and $\geq$5 severe (Buse et al. 2007, 2009).

MIBS-4 is collected at each monthly visit from baseline to the end of the study. The total score will be analyzed. Each item score and the level of interictal burden will be summarized.

5.4.3.5. European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L)

The European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire is a widely used, generic patient-rated scale that assesses current health status at the time of questionnaire completion, that is 'today' (The EuroQol Group 1990; Herdman et al. 2011). The questionnaire consists of 2 parts. The first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems). Answers to these 5 dimensions define a patient's health state. Given a patient's health state, the patient's country-specific health state index value can be obtained from the country-specific value set.

Country-specific value set is derived from valuation research that aims to measure how health is valued by people in a country. The valuation research includes a representative sample of participants from the general population in that country. In the valuation study participants are asked to value health by reviewing EQ-5D health states. The result from the valuation study is a value set for that country. The value set is essentially a set of weights to each of the levels in

each EQ-5D dimension. A high weight means that people in that country believe that such a score has a high impact on health-related quality of life.

The health state index value is a single value on a scale from less than 0 (where zero is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility.

The second part of the questionnaire consists of a visual analog scale (VAS) on which the patient rates their perceived health state from 0 (the worst health you can imagine) to 100 (the best health you can imagine).

The response to each question will be summarized. The health state index values (UK population based and US population based index values calculated based on the value sets @https://euroqol.org/wp-content/uploads/2018/02/EQ-5D-5L_Crosswalk_Value_Sets.xls) and VAS score will be analyzed.

5.4.3.6. Work Productivity and Activity Impairment Questionnaire (WPAI)

The Work Productivity and Activity Impairment Questionnaire (WPAI) is a patient-reported instrument developed to measure the impact on work productivity and regular activities attributable to a specific health problem (Reilly et al. 1993); for this study, the questions are specific to migraine. Recall period is the past 7 days. The scale contains 6 items that measure:

Q1) employment status,

Q2) hours missed from work due to migraine,

Q3) hours missed from work for other reasons,

Q4) hours actually worked,

Q5) degree migraine affected productivity while working (0-10, 0 –no effect, 10-completely prevent to work), and

Q6) degree migraine affected productivity in regular unpaid activities (0-10, 0 –no effect, 10-completely prevent me from doing).

Four scores are calculated from the responses to these 6 items as impairment percentages (Reilly et al. 1993), with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes.

- Absenteeism: Percent work time missed due to migraine (%) = Q2/(Q2 + Q4) *100 for those who were currently employed.
- Presenteeism: The Percent Impairment While Working due to migraine (%) = Q5*100/10 for those who were currently employed and actually worked in the past seven days
- The Percent Overall Work Impairment due to migraine (%) = (Q2/(Q2 + Q4) + (1 - Q2/(Q2 + Q4)) × (Q5/10))*100 for those who were currently employed;
- Activity Impairment: The Percent Activity Impairment due to migraine (%) = Q6*100/10 for all respondents.

The employment status will be summarized, and the four derived scores will be analyzed.

CCI

CCI [redacted]

5.4.4. Safety Endpoints

Safety endpoints consist of the incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and discontinuations due to adverse events (DCAEs), vital signs (blood pressure, pulse, and body temperature) and weight, electrocardiograms (ECGs), and laboratory measures (chemistry, hematology and urinalysis).

5.5. Statistical Analyses

5.5.1. General Considerations

Treatment effects will be evaluated based on an overall 2-sided significance level of 0.05 for all efficacy and safety analyses. The 95% confidence intervals (CIs) or standard errors for the difference in least-square means (LSMeans) between treatment groups will be provided.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the changes will be described in the SAP and/or in the clinical study report (CSR).

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or designee. SAS® software will be used to perform most or all statistical analyses.

5.5.1.1. Model Specifications and Adjustment for Covariates

This section specifies the general model terms and adjustment for covariates for different types of variables. For details of analysis methods, please refer to the specific sub-sections under Section 5.5.

Continuous Variables with Repeated Measures

Change from baseline of continuous variables with repeated measures will be analyzed using a mixed model repeated measures (MMRM) analysis. An MMRM analysis refers to a restricted maximum likelihood (REML)-based, mixed-effects repeated measures analysis using all the longitudinal observations at each postbaseline visit.

Unless otherwise specified, the MMRM will include the fixed, categorical effects of treatment, baseline migraine frequency category (low episodic migraine, high episodic migraine, and chronic migraine), pooled country, month, and treatment-by-month interaction, as well as the continuous, fixed covariates of baseline value and baseline value-by-month interaction. The baseline value and baseline-by-month interaction are included to account for the differential influence over time that the baseline value has on the postbaseline values. Rules for pooling countries are defined in Section 5.5.1.3. Pooled country and baseline migraine frequency category will be excluded in MMRM models for safety measures.

Continuous Variables Without Repeated Measures

For continuous variables without repeated measures, the change from baseline to LOCF endpoint will be analyzed using an analysis of variance (ANOVA) or an analysis of covariance (ANCOVA) model.

The ANOVA model for continuous efficacy / health outcome variables will contain the main effects of treatment, baseline migraine frequency category, and pooled country. The ANCOVA model for continuous efficacy / health outcome variables will contain the main effects of treatment, baseline migraine frequency category, pooled country, and appropriate baseline value.

When an ANOVA or ANCOVA model is used to analyze continuous safety variables, baseline migraine frequency category and pooled country will be removed from the model terms.

Unless otherwise specified, when ANOVA model or ANCOVA model is used, type III sum-of-squares for the LSMeans will be used for the statistical comparisons.

Binary Variables with Repeated Measures

Binary variables with repeated measures will be analyzed in generalized linear mixed models (GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis.

The GLIMMIX models for the repeated binary outcomes will include the fixed, categorical effects of treatment, month, baseline migraine frequency category, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value. When the fixed covariate of the continuous baseline value is the number of monthly migraine headache days, the baseline migraine frequency category will be excluded. Pooled country and the baseline value-by-month interaction will be excluded from the model in order to increase the likelihood of convergence.

Categorical Variables without Repeated Measures

For categorical efficacy variables without repeated measures, comparisons between treatment groups will be performed using logistic regressions. The logistic model will include the main effect of treatment, baseline migraine frequency category, and appropriate baseline value as a covariate.

For some health outcome variables without repeated measures during the double-blind treatment phase, as the scores of the categories (or number of events in HCRU) do not usually satisfy normal assumption, the change from baseline score will be analyzed using nonparametric tests:

Kruskal–Wallis test (Kruskal and Wallis 1952) for treatment comparison, and Wilcoxon Signed-rank test (Wilcoxon 1945) to compare the change from baseline within each treatment group.

For safety categorical variables and categorical variables of demographics and baseline characteristics, comparisons between treatment groups will be performed using Fisher's exact test as baseline migraine frequency is not expected to have an impact on the safety profile and does not have an impact on baseline measures.

5.5.1.2. Handling of Dropouts or Missing Data

Two statistical approaches to handling missing data will be used as appropriate: repeated measures analyses and ANCOVA/ANOVA model using change from baseline to LOCF endpoint.

For the repeated measures analyses, the model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when data are missing at random.

Please refer to Section 5.4.1 for approach to handling missing diary data for derivation of migraine headache days and other efficacy measures (with the exception of migraine attacks) derived from ePRO data per 30-day period.

Approaches to handling missing diary data for the derivation of migraine attack

For the derivation of the number of monthly migraine attacks, the LOCF method will be used to impute the missing ePRO diary days. If the patient was migraine headache-free on the day before the missing ePRO diary day, this would be carried forward as no migraine headache day until the actual next non-missing diary day. On the other hand, if the day before the missing ePRO diary day is a migraine headache day, then it would be carried forward as migraine headache day until the next non-missing diary day. The imputation will be carried out for all the missing diary days between the first non-missing to the last day.

If the diary compliance rate for a monthly interval is ≤50%, the number of monthly migraine attacks during that month will be considered missing. Please refer to Section 5.5.7 for diary compliance rate calculation.

5.5.1.3. Rules for Pooling Countries

All countries with fewer than 4 randomized patients in the placebo group or fewer than 4 randomized patients in the galcanezumab group with baseline and at least 1 postbaseline migraine headache day value will be pooled within region (North America, Europe, and Asia, as defined in Table CGAW.5.8) and considered as a single country for analyses.

All analyses will use pooled country when applicable. The investigative site numbers will be included in the listings.

5.5.1.4. Analysis Populations

There are 5 analysis populations defined:

Intent-to-treat (ITT) population: All patients who are randomized and receive at least 1 dose of study drug.

ITT episodic sub-population: All patients with episodic migraine who are randomized and receive at least 1 dose of study drug.

Safety population: This population is the same as the ITT population defined above.

GMB-treated population: All patients who have exposure to galcanezumab (GMB). The GMB-treated population will be used for summaries for GMB-treated time.

GMB-treated time is the period during which a patient received GMB.

- For patients who receive GMB in the double-blind treatment period (SP III) only, GMB-treated time begins and ends in SP III.
- For patients who receive GMB in both treatment periods, GMB-treated time begins in SP III and extends through SP IV.
- For patients who receive placebo in the double-blind treatment period, GMB-treated time begins in SP IV.

Open-label treatment population: All patients who enter the open-label treatment phase as indicated by receiving any injections starting from Visit 6. Analyses for open-label phase only will be based on the open-label treatment population.

Unless otherwise stated, all analyses will be conducted according to the ITT principle on the ITT population. That is, patients will be analyzed according to the treatment to which they were randomized, regardless of whether they actually received a different treatment.

Safety analyses and summary for exposure for the double-blind treatment phase will be conducted based on the modal treatment patients have received (placebo or GMB) during the double-blind treatment phase from the first dose at Visit 3 to the last dose at Visit 5. For determining modal dose:

- A dosing visit contributes to placebo if a patient receives no injections other than placebo. Otherwise, the dosing visit contributes to GMB in the modal dose calculation.
- Modal dose is the most frequent dose. If there is a tie, GMB will be used.

Safety and exposure data for GMB-treated time will be summarized.

5.5.1.5. Baseline and Postbaseline Definition

Table CGAW.5.4 describes the rules for determining the patient population and baseline and postbaseline observations for each study phase and type of analysis. When “last of Visit x-x” is used in the table, the last non-missing observation obtained in the visit interval will be used.

Table CGAW.5.4. Patient Population with Baseline and Postbaseline Definitions by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observation	Postbaseline Observation(s)
Study Period III			
Efficacy analyses (Repeated measures) or average of observed monthly values	ITT population and ITT episodic sub-population with a baseline and at least 1 postbaseline observation	Visit 3	All scheduled visits 3 < Visits ≤6
Efficacy analyses at LOCF endpoint		Visit 3	Last of Visit 3.01–6
Health outcome analyses (Repeated measures)		Visit 3	All scheduled visits 3 < Visits ≤6
Health outcome analyses at LOCF endpoint or for average of observed monthly values		Visit 3	Last of Visit 3.01-6
Treatment-emergent adverse events	Safety population	All Visits 1–3*a	All Visits 3.01–6
Serious adverse events, discontinuations due to adverse events	Safety population	NA	All Visits 3.01–6
Treatment-emergent abnormal laboratory values	Safety population with normal (with respect to direction being analyzed) laboratory values at all non-missing baseline visits and who have at least 1 postbaseline observation	Low: Min of Visits 1–3 High: Max of Visits 1–3 Abnormal: All Visits 1–3	Low: Min of Visits 3.01–6 High: Max of Visits 3.01–6 Abnormal: All Visits 3.01–6
Treatment-emergent changes in temperature and weight	Safety population with a baseline and at least 1 postbaseline observation	Low: Min of Visits 1–3 High: Max of Visits 1–3	Low: Min of Visits 3.01–6 High: Max of Visits 3.01–6
Treatment-emergent changes in blood pressures, pulse, and ECGs	Safety population with a baseline and at least 1 postbaseline observation	Low: Last of Visits 1–3 High: Last of Visits 1–3	Low: Min of Visits 3.01–6 High: Max of Visits 3.01–6
Continuous safety analyses (Repeated Measures)	Safety population with a baseline and at least 1 postbaseline observation	Last of Visits 1–3	All scheduled visits 3 < Visits ≤6
Continuous safety analyses – change from baseline to LOCF endpoint (ANCOVA)	Safety population with a baseline and at least 1 postbaseline observation	Last of Visits 1–3	Last of Visits 3.01–6

Patient Population with Baseline and Postbaseline Definitions by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observation	Postbaseline Observation(s)
Study Period IV			
Logistic regression – patients maintained 50% response	ITT population – GMB-treated in double-blind study phase	Visit 3	All scheduled visits 6 < Visits ≤9
Treatment-emergent adverse events by preferred term	Open-label treatment population	All Visits 1–6*a	All Visits 6.01–9
Study Periods III/IV Combined			
Efficacy/health outcome analyses	ITT population and ITT episodic sub-population with a baseline and at least 1 postbaseline observation	Visit 3	All scheduled visits 3 < Visits ≤9
Continuous safety analyses (Repeated Measures)	Safety population with a baseline and at least 1 postbaseline observation	Last of Visits 1–3	All scheduled visits 3 < Visits ≤9
GMB-Treated Time			
Treatment-emergent adverse events	GMB-treated population	All Visits 1–3 before double-blind phase dosing for patients treated with GMB during SP III; All Visits 1–6 before open-label phase dosing for patients treated with placebo during SP III*a	All visits after first dosing of GMB through Visit 9
Serious adverse events, discontinuations due to adverse events	GMB-treated population	NA	All visits after first dosing of GMB through Visit 9
Treatment-emergent abnormal laboratory values	GMB-treated population with normal (with respect to direction being analyzed) laboratory values at all non-missing baseline visits and who have at least 1 postbaseline observation	Visits 1–3 before double-blind phase dosing for patients treated with GMB during SP III; Visits 1–6 before open-label phase dosing for patients treated with placebo during SP III	All visits after first dosing of GMB through Visit 9: Visits 3.01–9 for GMB-treated patients during SP III; Visits 6.01–9 for placebo-treated patients during SP III

Patient Population with Baseline and Postbaseline Definitions by Study Period and Type of Analysis

Study Period/Analysis	Patient Population	Baseline Observation	Postbaseline Observation(s)
GMB-Treated Time			
Treatment-emergent changes in temperature and weight	GMB-treated population with a baseline and at least 1 postbaseline observation	Min/max of Visits 1–3 before double-blind phase dosing for patients treated with GMB during SP III for low/high, respectively; Min/max of Visits 1–6 before open-label phase dosing for patients treated with placebo during SP III for low/high, respectively	Min/max of all visits after first dose of GMB through Visit 9 for low/high, respectively: Visits 3.01–9 for GMB-treated patients during SP III; Visits 6.01–9 for placebo-treated patients during SP III.
Treatment-emergent changes in blood pressure, pulse, and ECGs	GMB-treated population with a baseline and at least 1 postbaseline observation	Last non-missing value from Visits 1–3 before double-blind phase dosing for patients treated with GMB during SP III; Last non-missing value from Visits 1–6 before open-label phase dosing for patients treated with placebo during SP III.	Min/max of all visits after first dosing of GMB through Visit 9 for low/high, respectively: Visits 3.01–9 for GMB-treated patients during SP III; Visits 6.01–9 for placebo-treated patients during SP III.

Abbreviations: AE = adverse event; ANCOVA = analysis of covariance; ECG = electrocardiogram; GMB = galcanezumab; ITT = intent-to-treat; LOCF = last observation carried forward; max = maximum; min = minimum; NA = not applicable; SP = study period.

*a, AEs that occurred on the visit date of Visit 3 or Visit 6 will be determined to be predose or after dose based on AE start time and the injection time: predose if AE start time is before the injection time and post dose if AE start time is after the injection time. Note: Visit 3.01 indicates the first unscheduled visit occurring after Visit 3 and prior to Visit 4. Visit 6.01 indicates the first unscheduled visit occurring after Visit 6 and prior to Visit 7.

5.5.2. Patient Disposition

The number and percentage of ITT patients who complete the study or discontinue early will be tabulated for all treatment groups for SP III and SP IV separately. Reasons for discontinuation will be compared between treatment groups using Fisher's exact test for SP III. Descriptive statistics only will be presented for the treatment groups in SP IV. In addition, subcategories of discontinuation due to subject decision will be summarized.

Patient allocation by investigator will be summarized for SP III for all ITT patients. Patient allocation by investigator will also be listed for all study periods.

5.5.3. Important Protocol Deviations

Important protocol deviations that potentially compromise data integrity or patients' rights or safety will be summarized by treatment group for the ITT population for SP II/III and for the open-label treatment population for SP IV.

Section 7 (appendix) lists the categories, subcategories, and study-specific terms of important protocol deviations, source of identification, and the method to identify each deviation. Per study team's discretion, for non-programmable protocol deviations, additional categories and subcategories other than the ones in Section 7 (appendix) can always be added to the final non-programmable protocol deviations list as deemed necessary.

Tables and listings of important protocol deviations for ITT population during all study phases will be provided by randomized treatment group.

5.5.4. Patient Characteristics

The following patient characteristics at baseline will be summarized by treatment group.

- Demographic (age, sex, ethnic origin, height, weight, BMI)
- Migraine and/or headache measures per 30-day baseline period:
  - number of migraine headache days
  - number of ICHD migraine headache days
  - number of headache days
  - number of migraine headache hours
  - number of headache hours
  - number of migraine attacks
  - number of monthly days with abortive medication use
  - number of migraine headache days with nausea and/or vomiting
  - number of migraine headache days with photophobia and phonophobia

  - number of migraine headache days with aura
  - number of migraine headache days with prodromal symptoms other than aura
- Number of prior migraine preventive medication categories failed in the past 10 years: 2, 3, or 4
- Patient Global Impression – Severity
- Alcohol, tobacco, caffeine, and nicotine consumption
- Medical history and preexisting conditions
- Presence of aura at baseline
- CCI [redacted]
- CCI [redacted]
- Contraindications to migraine preventive medications

Comparisons between treatment groups will be performed using Fisher's exact test for categorical data and ANOVA with treatment as independent variable in the model for continuous data.

Medical history and preexisting conditions will be summarized by descending frequency of preferred term (PT) within system organ class (SOC), and comparison between treatment groups will be performed using Fisher's exact test. Medical history is defined as illness(es) that ended prior to the signing of informed consent. Preexisting conditions and AEs at baseline are those AEs occurring during the baseline/screening visits for the study period, that is, Visit 1, Visit 2, and Visit 3.

5.5.5. Exposure to Investigational Medicinal Product

Patients will receive the investigational medicinal product (IMP) at the following planned time points:

- Beginning of Month 1 (Visit 3)
- Beginning of each month from Month 2 to Month 6 (Visit 4 to Visit 9)

The following information will be recorded on the eCRF for each dose:

- Confirmation that the patient received the IMP (including reason if the IMP was not given)
- Date and time of administration

The following will be derived from the information recorded on the eCRF:

- For SP III, duration of exposure in days is calculated as double-blind treatment phase disposition date – first date IMP administered +1.

- For SP IV, duration of exposure in days is calculated as open-label disposition date - first date IMP administered during SP IV +1.
- For SP III and SP IV separately, number and percentage of patients with 1 dose, 2 doses, and 3 doses injected.

Comparisons between treatments using the safety population for duration of IMP exposure will be performed using an ANOVA with treatment, baseline migraine frequency category, and pooled country in the model. The number of patients with 1 dose, 2 doses, and 3 doses will be summarized and treatment groups will be compared using Fisher's exact test. The number of patients with 1 dose, 2 doses, 3 doses, 4 doses, 5 doses, and 6 doses injected will be summarized for the GMB-treated population. In addition, injections not administered with the corresponding reasons will be listed.

Information about the use of comfort measures before or after the injection will be collected. The use of comfort measures will be summarized.

5.5.6. Treatment Compliance

Treatment compliance will be calculated for each treatment period (SP III and SP IV separately) as:

$$\frac{\text{number of doses received} * 100}{\text{number of intended doses}}$$

For this analysis, partial dose (for example, a patient only received 1 injection instead of 2 at Visit 3 or Visit 6) will be considered as no dose received.

For SP III, comparisons between treatments in the ITT population for treatment compliance will be performed using an ANOVA with treatment, baseline migraine frequency category, and pooled country in the model.

Treatment compliance for SP IV will be summarized similarly.

5.5.7. Electronic Patient-Reported Outcomes Diary Compliance

Electronic patient-reported outcomes diary compliance at each 1-month period (including baseline, Month 1, Month 2, … to Month 6) as well as for SP III overall (Month 1 through Month 3) will be calculated. Diary compliance at each 1-month period is calculated as:

$$\frac{\text{Actual number of diary days in the period}}{\text{Expected number of diary days in the period}} * 100$$

Expected number of ePRO diary days is calculated as date of injection at the end of the interval minus date of injection at the beginning of the interval +1.

For a patient who discontinues early in the double-blind (SP III) or open-label treatment phase (SP IV), compliance rate for the last month of that patient will be calculated with a denominator of 30 days (or the actual number of days in the interval if it is greater than 30).

Treatment comparisons for ePRO diary compliance for SP III will be performed using an ANOVA with treatment, baseline migraine frequency category, and pooled country in the model. ePRO diary compliance for SP IV will be summarized.

5.5.8. Previous Migraine Prevention Therapy

Prior Therapy: Migraine Preventives Lifetime

The proportion of patients with response to the previous migraine prevention therapy within each of the 6 categories (to enter this trial, medical history event, adequate response, inadequate response, no response, and treatment availability) will be summarized by medication. Treatment group comparisons will be done using Fisher's exact test. Previous migraine prevention therapies are those therapies that started prior to the date of the first injection and stopped prior to or on the date of first injection and the indication is "primary study condition."

Reasons for Discontinuation of Previous Migraine Prevention Therapy will be summarized by medication. If a patient discontinued the same medication multiple times with different reasons, the most recent reason will be included in the summary table.

The total number of medications that patients failed lifetime (derived from CRFs for both lifetime and past 10 years) will be calculated for each patient and will be summarized.

Prior Therapy: Failures during Past 10 Years

The proportion of patients who previously failed migraine prevention therapy (i.e., who discontinued the therapy due to "medical history event," "inadequate response," or "no response") in the past 10 years will be summarized by medication category. Treatment group comparisons will be done using Fisher's exact test. The reasons for failures will be summarized by medication within each medication category. If a patient failed the same medication multiple times with different reasons, the most recent reason will be included in the summary table.

The total number of medications that patients failed in the past 10 years that meet protocol inclusion criterion #4 (derived from the CRF for the past 10 years) and the total number of medications that patients failed in the past 10 years, including medications that do not meet inclusion criterion #4 (derived from the CRF for the past 10 years and the CRF for lifetime with an end date within past 10 years) will be calculated for each patient and will be summarized.

5.5.9. Concomitant Therapy

The proportion of patients who received concomitant medication recorded on the general concomitant eCRF will be summarized for the ITT population for SP III and SP IV separately, as will the proportion of patients who took abortive medications as recorded on the patient acute headache medication log, which will also be summarized separately for SP III and SP IV. Concomitant therapies for SP III are those that were stopped during SP III or continued in SP III. If a medication was started and stopped on the same day as the first injection, it will still be considered a concomitant medication for SP III. If a medication was started before the first day of injection but was stopped on the same day of injection, it will not be counted as concomitant

medication for SP III. Concomitant therapies for SP IV are those that were started, stopped, or continued in SP IV.

Treatment group comparisons will be done using Fisher's exact test for Study Period III. Only descriptive statistics will be presented for the treatment groups in Study Period IV.

5.5.10. Efficacy Analyses

5.5.10.1. Primary Outcome and Methodology

The primary objective of this study is to test the hypothesis that galcanezumab (120 mg per month with a 240-mg loading dose) is superior to placebo in the prevention of migraine headache in treatment-resistant migraine patients.

The primary analysis will evaluate the efficacy of galcanezumab compared with placebo on the overall mean change from baseline in the number of monthly migraine headache days during the 3-month double-blind treatment phase.

The primary analyses will be performed using a REML-based MMRM technique. The analysis will include the fixed categorical effects of treatment, pooled country, month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline number of migraine headache days and baseline-by-month interaction.

An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger (Kenward and Roger 1997) approximation will be used to estimate the denominator degrees of freedom. If the model does not converge with both the Hessian and the G matrix being positive definite under the default fitting algorithm used by PROC MIXED, the Fisher scoring algorithm will be implemented by specifying the SCORING option in SAS. If the model still fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met:

- Heterogeneous Toeplitz
- Heterogeneous First-order autoregressive
- Toeplitz
- First-order autoregressive

When the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle and Kenward 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is implemented by specifying the EMPIRICAL option in SAS®. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS®. SAS® PROC MIXED will be used to perform the analysis.

The primary endpoint of this study for galcanezumab compared with placebo will be estimated as the treatment main effect from the MMRM analysis model. This provides the average treatment effect across Month 1, Month 2, and Month 3. The Type I error rate for the study will

be controlled at a 2-sided 0.05 level (equivalently, 1-sided 0.025 level). Specific details of the testing procedure for the primary outcome and the secondary gatekeeper objectives are provided in Section 5.5.10.4.

The results of the statistical tests at each month in the double-blinded treatment phase will be used to assess the onset of effect for galcanezumab compared with placebo. In particular, if the primary efficacy analysis is statistically significant, then the earliest month where the statistically significant improvement is observed and maintained for all the subsequent months during the double-blinded treatment phase will be considered as the period that demonstrated the onset of effect. If the onset of effect occurs in Month 1, the number of weekly migraine headache days in Month 1 will be analyzed to identify the earliest week where the statistically significant improvement is observed and maintained for all the subsequent weeks in Month 1. Details about the analysis for the number of weekly migraine headache days are described in Section 5.5.10.3.

5.5.10.2. Sensitivity Analysis for Primary Outcome

Two types of sensitivity analyses are planned to assess the robustness of deviations from the assumptions of primary analysis including normality assumption and missing data assumption.

Missing Data Assumption

Sensitivity analyses will be performed to assess the robustness of the primary analysis conclusions to deviations from missing at random (MAR) assumption. The approach for these analyses is to vary the assumptions of missing data for the primary analysis in a systematic way. Basically, the method will predict the missing outcomes and then add values (Δ_{120}, Δ_P) to the predictions in the galcanezumab and placebo treatment groups respectively, regardless of the reason the data are missing. This approach is consistent with the sensitivity approach suggested in Permutt (2015). This procedure will be repeated multiple times for different values of (Δ_{120}, Δ_P) using the following steps:

1) Predict the missing outcomes for each treatment via multiple imputation based on observed primary endpoint and baseline values. Such imputation will be carried out using a Markov Chain Monte Carlo method with a Jeffreys prior via SAS® PROC MI. Thirty (30) such imputations will be created.
2) Add the corresponding Δ value (that is, Δ_{120}, Δ_P) to the imputed values based on the patient treatment group.
3) Conduct the primary analysis separately for each of the 30 imputations.
4) Combine the results of these analyses using Rubin's combining rules, as implemented in SAS® PROC MI ANALYZE.

The above steps will be repeated multiple times for different values of (Δ_{120}, Δ_P) with Δ_P ranging from 0 to twice the absolute value of the mean value seen for placebo in the primary analysis, Δ_{120} ranging from Δ^P to Δ_P + absolute value of the biggest mean treatment difference seen within the primary analysis. For example, if the overall mean change from baseline for placebo is -3.6 and the maximum overall treatment difference is -1.5, then Δ_P would range from 0 to7.2 and Δ_{120} would range from Δ_P to Δ_P + 1.5.

Normality Assumption

To assess the robustness of the MMRM results to deviations from normality assumption, a sensitivity analysis for raw number of migraine headache days (total number of migraine headache days for each interval without normalization to 30-day period) will be conducted with a repeated measures negative binomial regression model fitted with SAS PROC GLIMMIX. The model will include treatment, pooled country, month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline number of monthly migraine headache days and baseline-by-month interaction, log (number of compliant days within each month/30) as the offset in the model. In case of non-convergence, pooled country and/or baseline-by-month interaction may be excluded from the model. Directional consistency of treatment effects from this model and the primary analysis MMRM model as specified in Section 5.5.10.1 will be examined.

In addition, as another form of sensitivity analysis, residuals from the primary analysis MMRM model will be examined and outliers identified. Consistency of results before and after removing patients with outlier residuals will be examined.

5.5.10.3. Secondary and Exploratory Efficacy Analyses

Key secondary efficacy measures will be tested in the order as specified in Section 5.5.10.4

Table CGAW.5.5 summarizes all the planned secondary and exploratory efficacy analyses for SP III and SP III/IV, not including analyses for health outcome measures. Additional statistical analysis details are also provided below.

Continuous Efficacy Measures

For the continuous secondary efficacy measures, the change from baseline will be estimated from MMRM as described for analysis for primary outcome or ANCOVA as described in Section 5.5.1.1.

For continuous secondary efficacy measures where the objective is to assess overall mean change during 3-month double-blind treatment phase, the endpoint for galcanezumab compared with placebo will be estimated as the treatment main effect from the MMRM analysis assessing the average treatment effect across Months 1, 2, and 3.

Binary Efficacy Measures

For the repeated binary efficacy measures such as responder indicators based on the number of migraine headache days, the visit-wise binary outcomes indicating whether patients meet X% response criteria will be analyzed using a categorical, pseudo-likelihood-based repeated measures analysis. This analysis will be implemented using the GLIMMIX procedure in SAS to compare treatments with covariates adjustment described in Section 5.5.1.1.

An unstructured covariance structure will be used to model the within-patient errors (denoted by TYPE=CHOL in the RANDOM statement). The Newton-Raphson method with ridging will be used for nonlinear optimization (denoted by including NLOPTIONS TECH=NRRIDG). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If the

model does not converge, the Fisher's scoring algorithm will be utilized by the SCORING option in SAS.

If the model still fails to converge, the model will be fit using covariance matrices in the following order specified by a decreasing number of covariance parameters until convergence is met:

- Heterogeneous Toeplitz,
- Heterogeneous autoregressive,
- Toeplitz, and
- Autoregressive.

If necessary, both fitting algorithms will be used in the pre-specified order before proceeding to the next covariance structure in the sequence.

For models where the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle et al. 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is utilized by the EMPIRICAL option in SAS. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS.

For the binary secondary efficacy measures where the objective is to assess proportion of patients with X% response during the 3-month double-blind treatment phase, the endpoint for galcanezumab compared with placebo will be estimated as the treatment main effect from the categorical MMRM analysis assessing the average response rate across Month 1, Month 2, and Month 3.

The number of weekly migraine headache days in Month 1

If statistically significant improvement is observed at Month 1 and maintained for all the subsequent months during the double-blind treatment phase for the number of monthly migraine headache days, the number of weekly migraine headache days in Month 1 will be analyzed to identify the earliest week where the statistically significant improvement is observed and maintained for all the subsequent weeks in Month 1 for patients who have a monthly diary compliance rate greater than 50% for Month 1.

The number of weekly migraine headache days in Month 1 can be considered as ordinal data with possible values of 0, 1, 2, 3, 4, etc. and will be analyzed using an ordinal repeated measures model using the GLIMMIX procedure in SAS. In this model, a proportional odds model with cumulative logit link will be used, and a random intercept will be applied to the observations for each patient to account for repeated measures. The model will include the fixed, categorical effects of treatment, pooled country, week, and treatment-by-week interaction, as well as the continuous, fixed covariate of weekly baseline number of migraine headache days and weekly baseline number of migraine headache days-by-week interaction. Log (number of compliant calendar days within each week/7) will be included as the offset in the model. For weekly diary

compliance rate ≤50%, the number of weekly migraine headache days during that week will be considered missing.

The weekly baseline number of migraine headache days will be derived as (the monthly number of migraine headache days)/30*7.

Table CGAW.5.5. Secondary and Exploratory Efficacy Variables and Analysis Methods

Efficacy Variables	SP III	SP III/IV
Number of migraine headache days (episodic)	MMRM	MMRM
Number of migraine headache hours		
Number of migraine attacks (episodic only)		
Number of days with abortive medication use		
Number of days with triptan use		
Number of days with NSAIDs/aspirin use		
Number of days with acetaminophen/paracetamol use		
Number of days with ergot use		
Number of days with anti-nausea medication use		
Number of days with opioids and barbiturates use		
Number of headache days		
Number of headache hours		
Number of ICHD migraine headache days		
Number of migraine headache days with nausea and/or vomiting		
Number of migraine headache days with photophobia and phonophobia		
Number of migraine headache days with aura		
Number of migraine headache days prodrome symptoms other than aura		
Number of headache-free and symptom-free days		
Number of weekly migraine headache days in Month 1	GLIMMIX for ordinal outcome	NA
X% response rate (X=30, 50, 75, or 100)*a	GLIMMIX	GLIMMIX
Proportion of patients maintained 50% response in SP IV among all galcanezumab-treated 50% responders at Month 3	NA	Logistic regression
Global Patient Impression – Severity	ANCOVA	MMRM

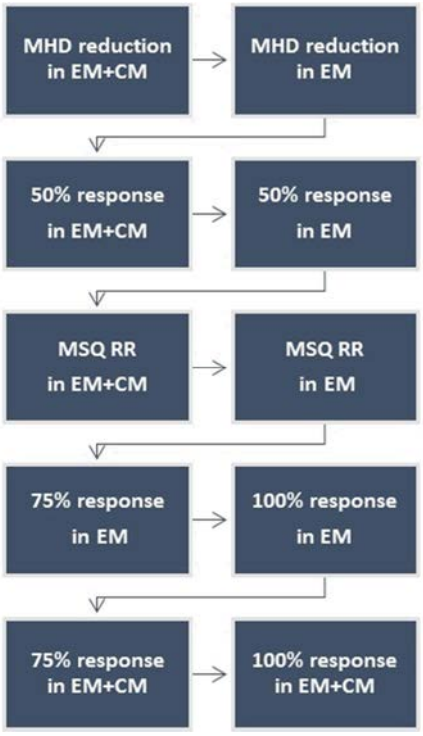
Abbreviations: ANCOVA = analysis of covariance; GLIMMIX = Generalized linear mixed model (for categorical variables); MMRM = Mixed models repeated measures; N/A= Not applicable.

*a 30% response rate is for chronic migraine subpopulation only.

5.5.10.4. Multiple Comparisons/Multiplicity

In order to provide strong control of the Type I error, the key secondary analyses will be tested using a gated testing approach at a 2-sided alpha level of 0.05. If the null hypothesis is rejected for the primary endpoint, key secondary endpoints will be sequentially tested following the gatekeeping hierarchy as shown in Figure CGAW.5.2.

Following the primary objective, the sequential procedure for key secondary objectives starts with the comparison between treatment groups in the number of migraine headache days based on ITT episodic subpopulation. If the null hypothesis is rejected for that comparison, then the comparison of 50% response rate between treatment groups will be tested in the ITT population. If that null hypothesis is rejected, then the next comparison in the sequence will be tested (50% response rate in the ITT episodic subpopulation), following this same pattern until all hypotheses are tested or until the null hypothesis is accepted for an endpoint, at which point, any further testing would stop for the key secondary objectives.



Abbreviations: CM = chronic migraine patients; EM = episodic migraine patients; MHD = the number of monthly migraine headache days; MSQ RR = Migraine Specific Quality of Life Questionnaire Role Function-Restrictive domain; response = response rate. See Section 5.4 for full definitions of endpoints. Note: All testing will be conducted at a 2-sided alpha of 0.05.

Figure CGAW.5.2. Gatekeeping sequence for testing of primary and key secondary endpoints.

5.5.11. Health Outcome Analyses

All health outcome measures will be analyzed or summarized for SP III, SP IV, and SP III/IV, if appropriate.

For MSQ (total score and 3 domain scores), MIDAS (total score and item scores), MIBS-4 (total score), WPAI (4 derived scores), EQ-5D-5L (UK population-based index value, US population-based index value, and VAS score), CCI [redacted]

- when there are repeated measures, they will be evaluated using MMRM as described in Section 5.5.10.1.
- when there is single post-baseline measure, they will be evaluated using ANCOVA model as described in Section 5.5.1.1.

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As HCRU data are count data with excess zeros for migraine patients, HCRU data will be summarized for the number of events per 100 patient years. Wilcoxon signed-rank test will be performed for comparisons within treatment group and Kruskal-Wallis test for comparisons between treatment groups.

Individual item scores of these health outcome questionnaire may be summarized if deemed necessary.

5.5.12. Safety Analyses

Unless specified otherwise, safety analyses outlined in the following subsections will be conducted on the safety population for SP III and on the GMB-treated population during the GMB-treated time; for SP III/IV, only the change from baseline with MMRM analysis will be conducted.

The safety and tolerability of treatment will be assessed by summarizing the following:

- Treatment-emergent adverse events (TEAEs)
  - By preferred term (PT)
  - By PT nested within system organ class (SOC)
  - By maximum severity
  - By considered to be related to investigational product by investigator
- Serious adverse events (SAEs) by PT
- AEs leading to discontinuation by PT
- Vital signs and weight

- Laboratory measurements
- ECGs

Additionally, TEAEs by PT will be conducted on the open-label population for SP IV only.

The baseline and postbaseline for all safety measures are described in Table CGAW.5.4 unless specified otherwise.

5.5.12.1. Categorical Safety Variables

Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits.

Comparisons between treatment groups for all categorical safety measures will be made using Fisher's exact test for SP III for the safety population. Only descriptive statistics will be presented for the analyses of the GMB-treated population.

5.5.12.1.1. Adverse Events

TEAEs are defined as the reported AEs that first occurred or worsened during the postbaseline phase compared with baseline phase. For each TEAE, the severity level of the event (mild, moderate, or severe) will be determined by patient or physician opinion. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. For each LLT, the maximum severity at baseline will be used as the baseline severity. If the maximum severity during postbaseline is greater than the maximum baseline severity, the event is considered to be treatment-emergent for the specific postbaseline period.

For each patient and TEAE, the maximum severity for the MedDRA level being displayed (PT, High Level Term, or SOC) is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level.

For events that are sex-specific, the denominator and computation of the percentage will include only patients from the specific gender.

5.5.12.1.1.1. Potential Hypersensitivity Events

Potential hypersensitivity events (immediate and non-immediate) will be identified from a search of preferred terms generated from the following queries:

- Anaphylactic reaction (SMQ 20000021)
- Broad and narrow terms in the Angioedema (SMQ 20000024)
- Broad and narrow terms in the Hypersensitivity (SMQ 20000214)

A listing of patients who reported an AE (TEAEs with all visits 1-3 as baseline, SAEs, and DCAEs) identified from these analyses will be medically reviewed to determine if the terms identified represent actual hypersensitivity events. Listings should include information on timing of event relative to latest dose of study drug administration, the event term from this query, other AEs for the patient and timing, any abnormal laboratory findings, and medical history. Only those that are judged medically to be hypersensitivity events will be included in the final tables.

The number and percentage of patients with TEAEs, SAEs, and AEs resulting in study drug discontinuation will be summarized by treatment groups using MedDRA PT nested within the SMQ. Events will be ordered by decreasing frequency within the SMQ.

The number and percentage of patients with treatment-emergent (TE) hypersensitivity events by maximum severity will be summarized by treatment groups using MedDRA PT.

The number and percentage of patients with TE hypersensitivity events by timing will be summarized using MedDRA PT. Events will be ordered by decreasing frequency. Note the timing of the hypersensitivity events is collected through eCRF and categorized into the following 4 categories:

- Immediate - occurs within minutes (<60 minutes) from study drug administration.
- Acute Reaction - occurs from 1 up to 6 hours from study drug administration.
- Delayed Reaction - occurs from >6 hours through 14 days from study drug administration, which will be split into 2 categories: on the same day of injection and after the day of injection.
- Reaction >14 days from study drug administration.

5.5.12.1.1.2. Adverse Events Related to Injection Sites

Adverse events related to injection sites will be defined using terms from the MedDRA High Level Term "Injection Site Reactions".

The number and percentage of patients with TEAEs related to injection sites, SAEs related to injection sites, and AEs related to injection sites resulting in study drug discontinuation will be summarized using MedDRA PT. Events will be ordered by decreasing frequency.

The number and percentage of patients with TEAEs related to injection sites by maximum severity will be summarized by treatment groups using MedDRA PT.

The number and percentage of patients with TEAEs related to injection sites by timing will be summarized using MedDRA preferred terms ordered by decreasing frequency. Note the timing of AEs related to injection sites is collected through eCRF and categorized into the same categories as for hypersensitivity events.

Adverse events related to injection sites will be summarized by whether comfort measures are used and what comfort measures are used.

Follow-up forms for adverse events related to injection sites will be summarized as well.

5.5.12.1.2. Vital Signs and Weight

Vital signs collected during the study include systolic and diastolic blood pressure (SBP and DBP), pulse, and temperature. Blood pressure and pulse measurements will be taken when the patient is in a sitting position.

The number and percent of patients meeting criteria for categorical changes of interest in vital signs and weight at any time during study will be summarized. Treatment group comparisons will be performed using Fisher's exact test.

Table CGAW.5.6 displays the criteria for categorical changes of interest in vital signs and weight. The last column of the table displays the patient populations defined by baseline categories.

The criteria to identify patients with treatment-emergent abnormal changes generally consist of a combination of two parts, an absolute threshold and a change from baseline amount.

- The absolute threshold in the criteria is based on 1) minimum postbaseline when the direction is low; 2) maximum postbaseline when the direction is high.
- The change from baseline amount in the criteria is 1) decrease from baseline (defined below and in Table CGAW.5.4) to minimum postbaseline when the direction is low; 2) increase from baseline (defined below and in Table CGAW.5.4) to maximum postbaseline when the direction is high.

The baseline for SBP, DBP, and pulse is defined as the last non-missing baseline value during the baseline period (See Table CGAW.5.4). To be exact,

- For analyses including double-blind treatment phase, the baseline for SBP, DBP, and pulse is defined as the last non-missing value before randomization.
  The rationale for using the last available value in the baseline period is to minimize the potential confound of discontinuing or dose stabilization of medications that modulate BP and pulse during the screening phase (which is early in the baseline period).
- Similarly, for GMB-treated time, the baseline is defined as the last non-missing value before patient's first dose of GMB. This baseline definition was chosen to be consistent with the analysis approach for double-blind treatment phase as described above.

This baseline definition for SBP, DBP, and pulse applies to all analyses (both continuous and categorical) for SBP, DBP, and pulse.

The baseline and postbaseline values for temperature and weight are defined in Table CGAW.5.4.

- For continuous analyses of temperature and weight, last non-missing baseline during the baseline period will be used as the baseline.
- For the analyses of categorical changes of interest in temperature and weight,
  - the baseline is defined as the minimum value during baseline period when the direction is low.
  - the baseline is defined as the maximum value during the baseline period when the direction is high.

Table CGAW.5.6. Criteria for Categorical Changes of Interest in Vital Signs and Weight

Parameter	Direction	Criteria	Patients Population defined by Baseline Categories
Systolic BP (mm Hg) (sitting)	Low	≤90 and decrease ≥20	All patients; >90; ≤90
	High	≥140 and increase ≥20	All patients; <140, ≥140
	PCS High	≥180 and increase ≥20	All Patients; <180; ≥180
	Sustained Elevation	≥140 and increase ≥20 at 2 consecutive visits	All patients; < 140; ≥140
Diastolic BP (mm Hg) (sitting)	Low	≤50 and decrease ≥10	All patients; >50; ≤50
	High	≥90 and increase ≥10	All patients; <90; ≥90
	PCS High	≥105 and increase ≥15	All Patients; <105; ≥105
	Sustained Elevation	≥90 and increase ≥10 at 2 consecutive visits	All patients; < 90; ≥90
Systolic BP or Diastolic BP (mm Hg) (sitting)	Sustained Elevation	Meeting criteria for systolic BP for 2 consecutive visits or meeting criteria for diastolic BP for 2 consecutive visits or both	All Patients
Pulse (bpm) (sitting)	Low	<50 and decrease ≥15	All patients; ≥50; <50
	High	>100 and increase ≥15	All patients; ≤100; >100
	Sustained Elevation	>100 and increase ≥15 at 2 consecutive visits	All patients; ≤100; >100
Weight (kg)	Low	(Loss) decrease ≥7%	All patients
	High	(Gain) increase ≥7%	All patients
Temperature (° F)	Low	<96° F and decrease ≥2° F	≥96°F
	High	≥101° F and increase ≥2° F	<101°F

Abbreviations: BP = blood pressure; bpm = beats per minute; F = degrees Fahrenheit; kg = kilograms; mm Hg = millimeters of mercury; PCS= Potentially Clinically Significant.

5.5.12.1.3. Electrocardiogram Intervals and Heart Rate

Analyses of corrected QT (QTc) interval will be calculated using Fridericia's correction formula, as $QT/RR^{1/3}$ (QTcF (msec)). For the QTcF calculation, the unit for QT is milliseconds and the unit for RR is seconds. For patients with QRS ≥120 msec at any time during the study, the QT and QTc interval will be excluded from the analyses. A listing of ECG data for patients with QRS ≥120 msec at any time during the study will be provided.

The baseline for ECG is defined as the last non-missing baseline value during the baseline period (See Table CGAW.5.4). To be exact,

- For analyses including double-blind treatment phase, the baseline for ECG is defined as the last non-missing value before randomization.
  The rationale for using the last available value in the baseline period is to minimize

the potential confound of discontinuing or dose stabilization of medications that modulate ECG during the screening phase (which is early in the baseline period).

- Similarly, for GMB-treated time, the baseline is defined as the last non-missing value before the patient's first dose of GMB. This baseline definition was chosen to be consistent with the analysis approach for the double-blind treatment phase as described above.

This baseline definition for ECG applies to all analyses (both continuous and categorical, quantitative and qualitative) for ECG.

The baseline and postbaseline values are summarized in Table CGAW.5.4.

The number and percent of patients meeting criteria for treatment-emergent abnormalities in ECG intervals (PR, QRS, and QTcF) and heart rate at any time during study will be summarized. Treatment group comparisons will be performed using Fisher's exact test.

Table CGAW.5.7 displays the criteria for treatment-emergent changes in ECG intervals and heart rate. The absolute threshold in the criteria is based on 1) minimum postbaseline when the direction is low; 2) maximum postbaseline when the direction is high.

- For treatment-emergent low analyses: Patients with all normal or high values at baseline (no low values) will be included.
- For treatment-emergent high analyses: Patients with all normal or low values at baseline (no high values) will be included.
- For treatment-emergent increase analyses: Patients with a baseline and at least 1 postbaseline result will be included.

Table CGAW.5.7. Criteria for Treatment-Emergent Changes in ECG Intervals and Heart Rate

Parameter	Direction	Criteria	
Heart Rate (bpm)	Low	<50 and decrease ≥15	
	High	>100 and increase ≥15	
PR Interval (msec)	Low	<120	
	High	≥220	
QRS Interval (msec)	Low	<60	
	High	≥120	
QTcF (msec)	Low	Males: <330	Females: <340
	High	Males: >450	Females: >470
	PCS High	>500 msec	
	Increase	Increase >30 msec	
		Increase >60 msec	
		Increase >75 msec	

Abbreviations: bpm = beats per minute; ECG = electrocardiogram; msec = milliseconds; PCS = potentially clinically significant; QTcF = Fridericia's corrected QT interval.

In addition, a descriptive summary of qualitative ECG abnormalities will be conducted which will include summaries of 11 ECG categories (Axis, Rhythm, Conduction, Ischemia, Infarction, Injury, Morphology, U-waves, T-waves, ST Segment, and Other Abnormalities) of qualitative findings at any time postbaseline. A category is a collection of possible descriptions (findings) of one qualitative aspect of an ECG. A category name is the name of the qualitative aspect of the ECG (for example, Rhythm, Conduction, Morphology, Ischemia, and so forth). A finding is 1 of the possible specific descriptions (for example, Sinus Bradycardia, Acute Septal Infarction) within a category.

A shift table summary of qualitative ECGs at any time will be produced to assess shifts from baseline normal to postbaseline abnormal for the overall ECG and for each of the 11 ECG categories mentioned above.

The summaries of the 11 ECG categories will exclude ECGs with any of the following: overall ECG could not be evaluated by the cardiologist, lead reversals or <9 leads, nonmatching demographic data, and those suggesting patient identification errors.

5.5.12.1.4. Laboratory Tests

The incidence rates of patients with treatment-emergent abnormal high or low laboratory values based on Covance reference ranges at any time postbaseline will be assessed using Fisher's exact test for each laboratory test for SP III.

Patients will be defined as having a treatment-emergent low value if they have all normal or high values at baseline, followed by a value below the lower reference limit at any postbaseline visit.

Patients with all normal or high values at baseline (no low values) will be included in the analysis of treatment-emergent low laboratory values. Patients will be defined as having a treatment-emergent high value if they have all normal or low values at baseline, followed by a value above the upper reference limit at any postbaseline visit. Patients with all normal or low values at baseline (no high values) will be included in the analysis of treatment-emergent high laboratory values.

For analytes simply classified as normal or abnormal, patients will be defined as having a treatment-emergent abnormal value if they have all normal values at baseline, followed by an abnormal value at any postbaseline visit. Patients with all normal values at baseline will be included in the analysis of treatment-emergent abnormal laboratory values.

The incidence of patients with the following elevations in hepatic laboratory tests at any time postbaseline will also be summarized. Comparison between treatment groups will be done for SP III using Fisher's exact test.

- The percentages of patients with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) measurement greater than or equal to 3 times (3×), 5 times (5×), and 10 times (10×) the Covance upper limit of normal (ULN) during the treatment period will be summarized for all patients with a postbaseline value.
- The percentages of patients with an Alkaline phosphatase (ALP) greater than or equal to 2 times (2×) the Covance ULN during the treatment period will be summarized for all patients with a postbaseline value.
- The percentages of patients with a total bilirubin (TBIL) measurement greater than or equal to 2 times (2×) ULN during the treatment period will be summarized for all patients with a postbaseline value.

Hy's law is defined as the combination of drug related elevation of ALT≥3× ULN and TBIL≥2× ULN, in the absence of significant cholestasis (that is ALP< 2× ULN), and in the absence of other causes of liver injury.

The analysis of elevation in ALT, AST, ALP, and TBIL will contain 3 subsets:

- patients whose non-missing maximum baseline value is less than or equal to 1× ULN for ALT, AST, ALP, and TBIL.
- patients whose non-missing maximum baseline value is greater than 1× ULN for ALT, AST, ALP, and TBIL , at the same time less than or equal to 2× ULN for ALT and AST, 1.5× ULN for ALP and TBIL.
- patients whose non-missing maximum baseline value is greater than 2× ULN for ALT and AST, 1.5× ULN for ALP and TBIL.

5.5.12.2. Continuous Safety Measures

Analyses of continuous safety data will be conducted for SP III and SP III/IV on patients who have a baseline and at least 1 postbaseline observation. In those analyses, values from

unscheduled visits will not be included, and only values collected at scheduled visits will be used.

For continuous safety measures (including laboratory measures, vital signs and weight, ECG intervals and heart rate), changes from last baseline value to LOCF endpoint during SP III, will be assessed using an ANCOVA model with treatment and baseline value as covariates. If repeat laboratory values exist at the same scheduled visit, only the last non-missing laboratory value at a visit (selected by using the variable with highest lab sequence ID) will be used in the ANCOVA analysis for mean change from last baseline value to LOCF endpoint.

For vital signs of blood pressure and pulse rate, as well as weight (when applicable), the mean change from baseline will be analyzed for SP III and SP III/IV using an MMRM analysis. The analysis will include the fixed categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline value and baseline-by-month interaction.

5.5.13. Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy measure (overall mean change from baseline in the number of monthly migraine headache days) only for the ITT patients in SP III. Table CGAW.5.8 provides definitions for each subgroup variable. Subgroup variables are usually selected if they are potentially prognostic or predictive. A subgroup variable is prognostic if values of the subgroup variable predict the change in efficacy measures regardless of the treatment group assignment. A subgroup variable is predictive if values of the subgroup variable predict heterogeneous treatment effect. Current understanding is that demographic subgroup variables (sex, racial origin, ethnicity, and region) are neither prognostic nor predictive, but they are standard subgroup variables needed for regulatory submission. The rest of the subgroup variables may potentially be prognostic. The purpose of the analyses for these subgroup variables is to assess the consistency of treatment effects across the different values of each subgroup variable.

For the subgroup variable of race, all the categories that have less than 10% of the patients in the study will be combined as 1 category. For the subgroup variable of region, if sample size in "other" region is less than 10% of total sample size, we will pull them into "Europe" region for subgroup analysis.

For the subgroup variable of age group, if >=65 age group has less than 10% of the patients in the study, it will be combined with the adjacent lower age group ([40,65)).

The subgroup-by-treatment interactions will be tested at a 2-sided 0.10 significance level. Treatment group differences will be evaluated within each category of the subgroup variable.

For all the subgroup variables, the subgroup analysis for change from baseline to each period in the number of migraine headache days will be conducted with MMRM. The same MMRM model as described in Section 5.5.1.1 will be used with terms of subgroup, subgroup-by-treatment, subgroup-by-month, and subgroup-by-treatment-by-month interactions added as

covariates. The LSMeans and LSMeans change estimate as well as the treatment comparisons within each subgroup will be analyzed with the data within that specific subgroup only. The MMRM model will be the same as described in Section 5.5.1.1.

Table CGAW.5.8. Definition of Subgroup Variables

Subgroup Variable	Categories
Sex	Male, female
Racial Origin (combine those with less than 10%)	American Indian / Alaskan Native Asian Black / African American Native Hawaiian / Pacific Islander White Multiple
Age	<40, [40,65), and >=65
Region	North America (United States, including Puerto Rico and Canada); Europe (UK, Netherlands, Spain, Italy, Czech Republic, Germany, France, Denmark, Hungary, and Belgium); Asia (Japan and Korea).
Baseline migraine frequency category	Low frequency episodic migraine, high frequency episodic migraine, or chronic migraine
Number of failed preventive migraine medication categories in past 10 years	2, 3, or 4

Other subgroup analyses may be conducted if deemed necessary.

5.5.14. Other Exploratory Analysis

Additional exploratory efficacy/safety analyses will be conducted as deemed necessary.

5.6. Interim Analyses

Interim analysis is planned when all randomized patients have had the chance to complete 3 months of double-blind treatment phase and, thus, will be the final analysis of the primary efficacy endpoint. Interim analysis will be conducted using internal unblinded study team members who do not have direct interaction with sites.

Depending on the outcome of the interim analysis, appropriate actions will be taken either to stop the study if galcanezumab is not efficacious or to stop or amend the study, if needed, due to a safety concern.

5.7. Unblinding Plan

Interim analysis will be conducted by unblinded study team members who do not have direct interaction with sites. All study personnel with direct interaction with sites will be kept blinded to the interim analysis results.

The study unblinded statistician will maintain a list of personnel involved in an internal data review (if applicable), the date and level of their unblinding, and a description of what subset of data, if not all the data, was shared.

A designated study team member in collaboration with the project statistician will be responsible for keeping a running log of individuals given access to any unblinded study data. This log will include the person's name, title, date of unblinding, level of unblinding (that is, group or patient), and purpose of unblinding.

5.8. Reports to be Generated at the Interim and Final Database Locks

5.8.1.1. Reports to be Generated at Interim Analysis

At the time of interim analysis, all randomized patients will have had the chance to complete 3 months of treatment. All analyses specified above for SP III will be generated at interim lock for ITT patients who have had a chance to complete 3 months of double-blind treatment. Additionally, the following analyses will be conducted for SP IV:

- Patient disposition as specified in Section 5.5.2
- Exposure to IMP as specified in Section 5.5.5
- ePRO diary compliance as specified in Section 5.5.7
- TEAEs
- Important protocol deviations
- Primary and key secondary efficacy analyses as specified in Section 5.5.10

Analyses conducted at interim analysis for SP III will be considered as the final analyses for the double-blind treatment phase and will be used in the final CSR.

5.8.1.2. Report to be Generated at Final Database Lock

All reports that have not been generated as part of the interim analyses or that did not contain final data at the time of the interim analysis (i.e., any reports based on SP IV or SP III/IV) will be generated at final database lock. Reports from the double-blind treatment period will be final at the interim analysis and therefore will not be rerun for the final database lock.

5.9. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements. These analyses will be the responsibility of the Sponsor.

Analyses provided for the CTR requirements include the following:

A summary of AEs will be provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE.

- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
  - the number of participants at risk of an event
  - the number of participants who experienced each event term
  - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients in every treatment group may not be included if a 5% threshold is chosen.
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

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7. Appendix: Description of Important Protocol Deviations

Appendix Table 1. Description of Important Protocol Deviations

Category	Subcategory	Study-Specific	Source	Comments
ICF	ICF not obtained	Initial ICF date is missing or is after (Visit 1 date or Visit 1 lab date)	Programmable - Stats	
	Improper ICF	ICF not signed prior to initiation of protocol procedures	Non-programmable - Monitor identified	
Eligibility	Inclusion/ Exclusion	Age <18 or >75 years old at study entry	Non-programmable- Monitor identified	
		Number of migraine headache days <4 per 30-day period at baseline	Programmable - Stats	Based on normalized number of migraine headache days.
		Number of headache-free days <1 at baseline	Programmable - Stats	Based on normalized number of headache days.
		Baseline ePRO compliance <80%	Programmable - Stats	
		Number of migraine preventive medication treatment failure categories in the past 10 years is <2 or >4	Programmable - Stats	
		Female patients have a positive serum pregnancy test prior to randomization visit	Programmable - Stats	
		Female patients have no serum pregnancy test prior to randomization visit	Non-programmable-Monitor identified	

(To be continued)

Description of Important Protocol Deviations (continued)

Category	Subcategory	Study-Specific	Source	Comments
Eligibility	Inclusion/ Exclusion	Insufficient washout of prohibited migraine preventive medication for at least 5 days prior to Visit 2	Programmable - Stats	Patients must have discontinued such treatment at least 5 days prior to Visit 2.
		Insufficient Washout of Botulinum toxin A and B at least 3 months prior to Visit 2 if for therapeutic use	Non-Programmable-Study Team identified	1) Stats will create the list of patients who meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable Excel spreadsheet. 3) A month may be defined as 4 weeks.
		Insufficient Washout of Nerve Block or Device Use in the head or neck area or for migraine prevention at least 30 days prior to Visit 2	Non-Programmable-Study Team identified	1) Stats will create the list of patients who meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable Excel spreadsheet.
		Other inadvertent enrollment which is deemed clinically important by Lilly Medical	Non-Programmable-Study Team identified	Not all inadvertent enrollments will necessarily be considered clinically important.
Data Quality	Missing Data	Diary compliance <=50% for half or more of patient's double-blind treatment phase participation	Programmable – Stats	With <=50% ePRO compliance rate for half or more months of double blind treatment phase, where "month" refers to a dosing interval. For example, • if patient remained in the study for 3 months (i.e., dose intervals), and >=2 months have ePRO compliance <=50%. • if patient remained in the study for 1 or 2 months (i.e., dose intervals), and >=1 months have ePRO compliance <=50%.
				Lost to follow-up patients' last month interval should not be included in the consideration above.
				If a patient discontinued before Visit 4 or if total time in double-blind period was less than 2 weeks, the patient should not be counted here.

(To be continued)

Description of Important Protocol Deviations (continued)

Category	Subcategory	Study-Specific	Source	Comments
Data Quality	Missing Data	Missing safety measurement: vital signs (Blood pressure, body temperature, pulse) at baseline or in SP III	Programmable – Stats	For randomized patients with non-missing Visit 4 date, if blood pressure, body temperature, or pulse are missing all baseline or missing all post-baseline measures during the double-blind treatment period. For patients who discontinued due to "lost to follow up", if all postbaseline measures are missing, it is not an important protocol deviation
		Missing safety measurement: Chemistry or Hematology at baseline or in SP III	Programmable – Stats	For randomized patients, if calcium and hemoglobin are missing all baseline measures, or if there is non-missing Visit 6 date and missing the post-baseline measures in the double-blind treatment period. For patients who discontinued due to "lost to follow up", if all post-baseline measures are missing, it is not an important protocol deviation.
		Missing safety measurement: ECGs at baseline and in SP III	Programmable – Stats	Same rule as for "Missing safety measurement: Chemistry or hematology at baseline or in SP III".
Study Procedures	Excluded Conmeds	Taking prohibited migraine preventive medication for primary study indication for >7 consecutive days during SP II or SP III	Programmable - Stats	Prior therapy should be excluded in the consideration.
		Taking prohibited migraine preventive medication for primary study indication for >7 consecutive days during SP IV		
		Taking prohibited migraine preventive medication for any indication for >7 consecutive days during SP II or III	Programmable - Stats	Prior therapy should be excluded in the consideration.
		Taking prohibited migraine preventive medication for any indication for >7 consecutive days during SP IV		
		Taking Botulinum toxin A and B in the head or neck for therapeutic indication during SP II, III, or IV	Non-Programmable - Study Team identified	1) Stats will create the list of patients who meet this IPD criteria. 2) Among those, the true IPDs will be manually added into non-programmable excel sheet.
		Opioid, barbiturate, or steroid use >7 consecutive days during SP II or III		
		Opioid, barbiturate, or steroid use >7 consecutive days during SP IV	Programmable - Stats	Prior therapy should be excluded in the consideration.

(To be continued)

Description of Important Protocol Deviations (continued)

Category	Subcategory	Study-Specific	Source	Comments
Investigational Product	Medication not fit for use	Patient received drug that was declared "Not Fit for Use"	Non-Programmable - Monitor identified	
	Dosing Error	Significant violations of study drug dosing	Non-Programmable - Monitor identified and Study Team identified	1) Stats will create the list of patients who have incorrect dosing (not including skipped dose). 2) Monitors will identify other events not able to be captured by programming (such as switched IP packages) 3) Medical will review both lists and identify IPDs to be manually added into non-programmable Excel sheet.
	Injection Schedule	Skipped dose of study drug	Programmable - Stats	
	Unblinding	Unjustified unblinding of patient treatment assignment	Non-programmable - Monitor identified	
Administrative/ Oversight	Suspected misconduct	Suspected Fraud	Non-programmable - Monitor identified	
	Patient privacy violation	Privacy Breach	Non-programmable - Monitor identified	This will only include those events which result in a full de-identification of the patient.
Safety	Other	Site did not appropriately report SAE	Non-programmable - Monitor identified	Failure to report an SAE within a reasonable timeframe relative to the requirement of within 24 hours of the investigator being made aware of the SAE (for example 28 hours would not be an important deviation); Failure to respond to SAE queries.
		Dosed female has positive pregnancy test during the treatment phase and not discontinued from treatment	Non-programmable - Monitor identified	

Abbreviations: Conmeds = concomitant medications; ECG = electrocardiogram; ePRO = electronic patient-reported outcome; ICF = inform consent form; IP = investigational product; IPD = important protocol deviation; SAE = serious adverse event; SP = study period.

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